REMARKS

Claim Amendments

Claims 1-107 are currently pending in the application. Claims 43-50, 52, 53 and 55-107 are withdrawn from consideration. Claims 1-42, 51 and 54 are currently under consideration. Claims 1-42, 51 and 54 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

35 U.S.C. §112 first paragraph rejection

The Office Action states that claims 1, 3-42, 51 and 52 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventor(s) had possession of the claimed invention at the time the application was filed. Namely, the Examiner points to the phrase "comprising amino acid residues 77-95 of SEQ. ID. NO.: 10", as is recited in claims 1, 6, 15, 20, 29 and 34 as representing a departure from the specification and the claims as originally filed, and further asserts that the limitation does not find support within the specification.

First, Applicants submit that a mutant fragment comprising amino acids 77-95 of Tumstatin is supported on page 48 of the Specification (See, for example, "TP3" in Table 1). However, in order to expedite prosecution and without acquiescing to the Examiner's rejections, Applicants herein amend claims 1, 6, 15, 20, 29 and 34 to recite a peptide "of SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45." For example, claim 1 is amended to recite:

1. An isolated Tumstatin polypeptide of SEQ. ID. NO.: 33 or a fragment thereof comprising the sequence of SEQ. ID. NO.: 45, and having the ability to inhibit tumor growth.

The peptide of SEQ. ID. NO.: 33, also referred to as Tum-1, finds support within the specification, including Figures 34, 35, and on Page 47 (Table 1). Applicants submit that the sequence of SEQ. ID. NO.: 45 has been extensively described within the specification. For example, page 62 describes the alignment of numerous peptide fragments, from which a

consensus or "generic" sequence was derived. In addition, Applicants submit that fragments of SEQ. ID. NO.: 33 comprising the sequence of SEQ. ID. NO.: 45 finds extensive support in the specification (See, for example, Tumstatin-45-132 (SEQ. ID. NO.: 33); Tum-5 (SEQ. ID. NO.: 26); T3 (SEQ. ID. NO.: 29); and T7 (SEQ. ID. NO.: 37)).

As amended herein, claims 1, 6, 15, 20, 29 and 34, as well as claims 3-5, 7-14, 16-19, 21-28, 30-33, and 35-42, which depend from these claims, recite subject matter which is described in the amended specification, in fulfillment of the written description requirement under 35 U.S.C. §112, first paragraph. As such, Applicants respectfully request withdrawal of this rejection under §112, first paragraph.

Claims 2, 6-9, 20-23 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, for lack of enablement, because the specification, "while enabling for an isolated fragment of SEQ. ID. NO.: 37, having the ability to inhibit tumor growth, inhibit angiogenesis and inhibit protein synthesis in endothelial cells, SEQ. ID. NO.: 38 having the ability to inhibit protein synthesis in endothelial cells, and SEQ. ID. NO.: 39-42 having the ability to inhibit tumor growth, does not allegedly reasonably provide enablement for an isolated mutated fragment comprising amino acid residues 77-95 of SEQ. ID. NO.: 10, wherein one or more, and five or fewer, amino acids have been substituted, and wherein the mutated fragment has the ability to inhibit tumor growth in claims 6, inhibit angiogenic activity in claim 20 or inhibit protein synthesis in claim 34, wherein the mutated fragment is reduced in claims 7, 21, 35, wherein the fragment is alkylated in claims 8, 22 and 36, wherein the fragment is oxidized in claims 8, 22 and 37, or an isolated polypeptide "having" the amino acid sequence of SEQ. ID. NO.: 37 in claim 2."

Applicants respectfully disagree. As described above, Applicants amend herein claims 1, 6, 15, 20, 29 and 34 to recite a polypeptide "of SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45..." Thus, the claims no longer recite the "amino acid residues 77-95" limitation. Applicants submit that the specification is fully enabling for the polypeptide of "SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45..."

With respect to the Examiner's rejection of claim 2, Applicants assume that the rejection pertains solely to the term "having", as stated on page 3, second paragraph of the Office Action.

Applicants respectfully request clarification if the claim is rejected on additional grounds. Applicants herein amend claim 2 to depend from claim 1. As claim 2 now incorporates the limitations of claim 1, the polypeptide recited in claim 2 is not open-ended. As such, Applicants assert that claim 2, as is currently amended, is enabled, and as such respectfully request reconsideration.

The Examiner further asserts that, as claims 6, 20 and 34 recite "one or more, and five or fewer amino acids" substitutions of SEQ. ID. NO.: 10, "the claims provide up (5X19)95 substitutions (for naturally occurring amino acids), not all which are necessarily predictive of inhibiting tumor growth, angiogenic activity or protein synthesis in endothelial cells." The Examiner concludes that the invention as claimed would require a level of experimentation that is excessive and undue.

Applicants have amended claims 6, 20, and 34 such that they no longer recite the "one or more, and five or fewer" limitation with respect to SEQ. ID. NO.: 10, but the limitation of "further comprising one to five substitutions" is present in the claim as herein amended. To the extent that the rejection may be applicable as amended, Applicants respectfully disagree with the Examiner's assertion. Applicants respectfully refers the Examiner to *Ex parte Mark* (12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int. 1989). In this case, the broadest appealed claim was as follows:

> 1. A synthetic mutein of a biologically active native protein in which the native protein has at least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues substituted by another amino acid and said mutein exhibiting the biological activity of said native protein.

Id., at 1905. The claim in *Mark* thus covers a mutant protein containing an amino acid that has been substituted for a non-essential cysteine residue. The specification at issue in that case set forth three working examples in which it was shown that each of three proteins had a non-essential cysteine residue which could be deleted or replaced, with retention of biological activity in the resulting mutein.

The Examiner in *Mark* raised two overbreadth issues with respect to this claim: (1) whether the specification supported a claim broad enough to encompass any mutant protein and (2) whether the specification supported a claim broad enough to encompass substitution of any cysteine residue within the protein. The Examiner's reasons for rejecting the broad claim in *Mark* were as follows:

> Essentially, the position taken in the rejection is that it would require undue further experimentation to construct by recombinant methods (site specific mutagenesis) the innumerable muteins encompassed by the instant claims (claims encompass modification of any protein which comprises a "non-essential" cysteine residue) and to screen the muteins produced for any of those which exhibit biological activity after modification.

Id., at 1906. The Examiner also stated that the claims were broad enough to "encompass any protein, even those which have not been characterized or cloned." *Id.*, at 1906.

The Board of Appeals disagreed with the Examiner's analysis and concluded that the claim was enabled for all cysteine-depleted muteins of biologically active proteins in which the mutein retains the biological activity of the native protein. The Board reframed the enablement issue and reasoned that the record established that, for a given protein having cysteine residues, one skilled in the art 1) would be able to substitute for or delete the cysteine residues as desired, and 2) could routinely determine whether deletion or replacement of cysteine residues in a given instance in fact resulted in an operative mutein falling within the claims. Upon applying this framework to the specification and claims before them, the Board concluded that, although some cysteine-depleted muteins may not be operable, the disclosure was enabling for the claims, since one skilled in the art was (1) clearly enabled to perform the work that was needed to produce any given mutein falling within the description in the claims and (2) to determine whether the cysteine depleted construct retained the biological activity of the native protein.

Applicants submit that the rationale applied and decision rendered by the Board in *Ex parte Mark* is directly applicable to the present situation. That is, for a given polypeptide of SEQ. ID. NO.: 33 or a fragment thereof comprising the sequence of SEQ. ID. NO.: 45, one skilled in the art (1) would be able to make one to five substitutions, and (2) could routinely determine

whether the substitution in a given polypeptide in fact resulted in a polypeptide having anti-tumor, anti-angiogenic, or endothelial protein synthesis inhibiting activity. The specification provides extensive guidance as how to modify the polypeptides, as well as how to test whether such mutated polypeptides inhibit tumor growth, angiogenic activity, and protein synthesis. Such guidance can be found in the instant application, for example on page 63, line 16 to page 64, line 13, as well as in Example 23: "Recombinant Production of Tumstatin and Tumstatin Mutants in E. coli", and Example 35: "Recombinant Production of Tumstatin Mutants Tum-1, Tum-2, Tum-3 and Tum-4" which describe how to generate mutants/fragments of Tumstatin. In addition, just a small sample of the extensive guidance provided within the specification in how to test an isolated mutated fragment for:

1. Inhibition of tumor growth (See, for example, Example 30: "Tumstatin and Tumstatin Mutant Inhibit Tumor Growth in vivo"; Example 46: "Effect of Tumstatin-45-132 on Angiogenesis and Tumor Growth"; Example 56: "Activity of T8 Synthetic Peptide in a MDAMB-435 Tumor Xenograft Model"; Example 57: "Activity of T8 and TP3 Synthetic Peptides Against a MDAMB-435 Tumor Xenograft Model"; Example 58: "Activity of T7, T8, TP3, SP1 and SP2 Synthetic Peptides in a PC3 Tumor Xenograft Model"; Example 59: "Activity of T8, T8-3, P2, and SP2 Synthetic Peptides in MDAMB- 435 Tumor Xenograft and PC3 Tumor Xenograft Models");

2. Inhibition of angiogenic activity (See, for example, Example 50: "Comparison of Anti-Angiogenic Activity of Tumstatin and Deletion Mutants"; Example 51: "In Vivo Anti-Angiogenic Activity of Synthetic Peptides"; Example 40: "Activities of Synthetic Fragments of Tumstatin"; Example 41: "Activity of Deletion Mutants of Tumstatin"; Example 43: "Activities of Tumstatin-45-132 and Tum-5-126-C-A"; Example 45: "Binding Activity of Tumstatin-45-132");

3. Inhibition of protein synthesis (See, for example, Example 52: "Tumstatin Peptides Inhibit Total Protein Synthesis in Endothelial Cells"; Example 53: "Tumstatin Peptides Inhibit Cap-Dependent Protein Translation in Endothelial Cells"; Example 54: "The

Endothelial Cell Specific Inhibitory Effect of Tumstatin Peptides on Cap-Dependent Translation and Protein Synthesis is Mediated Via $\alpha\nu\beta3$ Integrin")

Furthermore, the specification provides support for the situation in which the fragment is reduced (See for example, page 50, lines 15 to 24; and Example 43: "Activities of Tumstatin-45-132 and Tum-5-126-C-A"); the situation in which the fragment is alkylated (See for example, page 54, lines 1 to 9; page 68, lines 16 to 24; and Example 43: "Activities of Tumstatin-45-132 and Tum-5-126-C-A"); and the situation in which the fragment is oxidized (See, for example, Example 49: "Synthesis and Activity of T3 Folded Peptide and S--S Bridge Formation").

Applicants therefore submit that there is sufficient guidance in the specification such that obtaining Tumstatin polypeptides falling under the recited claims would not require a level of experimentation that is excessive and undue. As such, Applicants respectfully request withdrawal of this §112, first paragraph, rejection of these claims.

35 U.S.C. §102 rejection

The Examiner has further rejected claim 1-2, 6, 15, 20, 29, 34, 51 and 54 under 35 U.S.C. §102(b) as allegedly being anticipated by Kalluri et al (J Biol. Chem. 271: 9062-9068, 1996). The Office Action states:

> "Kalluri et al. further teach a deletion of N-terminal triple helix 26 aa and C-terminal 36 amino acid (α3/n-26/c-36). Kalluri et al further teach mutated fragment, α3/n-26/c-KK having a deletion of N-terminal triple helix 26 aa and substitution of last two lysines to alanine (see the entire document and page 9064 under Figure 1 in particular). While the prior art teachings may be silent as to the ability to 'inhibit tumor growth', 'inhibit angiogenic acitivity', 'inhibit protein synthesis in endothelial cells', the protein synthesis is 'cap-dependent protein synthesis' and the endothelia cells 'express αvβ3 integrin' per se; the product in Kalluri et al reference is the same as the claimed product. Therefore 'inhibit tumor growth', 'inhibit angiogenic acitivity' and 'inhibit protein synthesis in endothelial cells' are considered inherent properties."

Claims 1, 6, 15, 20, 29, 34 are amended herein to recite a peptide "of SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45..." Applicants submit that the polypeptide of SEQ. ID. NO.: 33 encompasses amino acids 54 – 244 of SEQ. ID. NO.: 10.

Kalluri et al. do not disclose or suggest a peptide "of SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45..." Furthermore, claim 2 is amended to depend from claim 1, and would therefore include the limitations of claim 1.

As such, Applicants submit that the claims as amended are novel over Kalluri et al. Applicants respectfully request reconsideration of the claims.

35 U.S.C. §103 Rejections

The Examiner has issued obviousness type rejections over the instant claims. Namely:

Claims 1, 3, 6-7, 15, 17, 20-21, 29, 31 and 34-35 are rejected under 35 U.S.C. §103(a) over a combination of Kalluri et al. and U.S. 5,858,670 ('670). The Examiner asserts that Kalluri et al. disclose all the elements of these claims except for reducing the fragments, a deficiency which the '670 reference is said to provide.

Claims 1, 4, 6, 8, 15, 18, 20, 22, 29, 32, 34 and 36 are rejected under 35 U.S.C. §103(a) over a combination of Kalluri et al. and U.S. 5,326,875 ('875). The Examiner asserts that Kalluri et al. disclose all the elements of these claims except for alkylation of the fragment, a deficiency which the '875 reference is said to provide.

Finally, claims 1, 5, 6, 9, 15, 19-20, 23, 29, 33-34 and 37 are rejected under 35 U.S.C. §103(a) over a combination of Kalluri et al. and U.S. 5,807,821 ('821). The Examiner asserts that Kalluri et al. disclose all the elements of these claims except for oxidation of the fragments, a deficiency which the '821 reference is said to provide.

Claims 1, 6, 15, 20, 29, and 34 are amended herein to recite a polypeptide "of SEQ. ID. NO.: 33 or fragments thereof comprising the sequence of SEQ. ID. NO.: 45." Kalluri et al. does not disclose or suggest the polypeptide as recited in these claims. This deficiency is not remedied by any of the above combination references ('670, '875, and '821 patents). As such, Applicants submit that the combinations cited by the Examiner are not sufficient to render the instant claims obvious, and as such, respectfully request reconsideration of the claims.

Conclusion

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

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